American Journal of Epidemiology

Vol. 160, No. 7
Printed in U.S.A.
DOI: 10.1093/aje/kwh267

Toenail Arsenic Content and Cutaneous Melanoma in Iowa

Laura E. Beane Freeman[1,2], Leslie K. Dennis[2], Charles F. Lynch[2], Peter S. Thorne[3], and Craig L. Just[4]

[1] Division of Cancer Prevention, National Cancer Institute, Bethesda, MD.
[2] Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA.
[3] Department of Occupational and Environmental Health, College of Public Health, University of Iowa, Iowa City, IA.
[4] Department of Civil and Environmental Engineering, University of Iowa, Iowa City, IA.

Received for publication August 28, 2003; accepted for publication April 8, 2004.

Cutaneous melanoma has the lowest survival rate of all forms of skin cancer. There has been little research investigating the link between arsenic and cutaneous melanoma, although arsenic has been associated with increased risk of nonmelanoma skin cancer. The authors performed a case-control study examining the association between cutaneous melanoma and environmental arsenic exposure among Iowans aged 40 years or older. Participants included 368 cutaneous melanoma cases and 373 colorectal cancer controls diagnosed in 1999 or 2000, frequency matched on gender and age. Participants completed a mailed survey and submitted toenail clippings for analysis of arsenic content by graphite furnace atomic absorption spectrophotometry. The authors found an increased risk of melanoma for participants with elevated toenail arsenic concentrations (odds ratio = 2.1, 95 percent confidence interval: 1.4, 3.3; *p*-trend = 0.001) and effect modification by prior skin cancer diagnosis (*p*-interaction = 0.03). The arsenic-melanoma findings in this study are not known to have been previously reported in observational epidemiologic studies involving incident cutaneous melanoma. Therefore, the findings warrant confirmation.

arsenic; case-control studies; melanoma; skin neoplasms

Abbreviations: CI, confidence interval, OR, odds ratio

The incidence of cutaneous malignant melanoma is increasing, and the annual percentage change is one of the highest for all cancers in the United States (1). It is estimated that 54,200 cases of cutaneous melanoma were diagnosed and 7,600 deaths were attributed to melanoma in the United States in 2003 (1).

Arsenic is a naturally occurring metalloid element. Commercial use of arsenical compounds in various industries was common (2, 3) but has declined in more recent years (4). Water contamination can occur naturally when arsenic-rich ores leach into ground- and surface water (5). Some areas in Iowa have high levels of arsenic in the water supplies. One survey by the Iowa Department of Natural Resources estimated that up to 12 percent of Iowa's municipal water supplies include wells or sources of water with arsenic concentrations greater than or equal to 10 μg/liter (6). In this subset of supplies with high concentrations, the highest concentration detected was 80 μg/liter and the average concentration was 21 μg/liter. The arsenic concentration in private wells is less well characterized because there are no regulatory databases to capture this information. A recent US Geological Survey project sampled wells and compiled data to estimate arsenic concentrations in groundwater, including private wells. Because of insufficient data for Iowa, it is not possible to estimate the arsenic concentration in groundwater by using this database (7).

A number of epidemiologic studies and case reports link arsenic with the development of skin cancer (3, 8–11). Many of these studies were based on ecologic data from Taiwan, where levels of arsenic were much higher (10, 12) than most estimates in the United States (4). Extrapolation from risk assessments of highly exposed populations has indicated that arsenic levels as low as 2 μg/liter may be carcinogenic (13). A New Hampshire study (9) attempted to quantify exposure

Reprint requests to Dr. Laura Beane Freeman, Occupational and Environmental Epidemiology Branch, National Cancer Institute, 6120 Executive Boulevard, EPS 8121, MSC 7240, Bethesda, MD 20892-7240 (e-mail: freemala@mail.nih.gov).

to arsenic in relation to development of nonmelanoma skin cancer. The authors reported odds ratios of 2.07 (95 percent confidence interval (CI): 0.92, 4.66) and 1.44 (95 percent CI: 0.74, 2.81) for squamous cell carcinoma and basal cell carcinoma, respectively, for the highest category of arsenic (9). To our knowledge, there have been no studies of arsenic exposure and melanoma incidence, although ecologic data and mortality studies have suggested a potential link between elevated arsenic levels and melanoma (2, 14, 15).

Arsenic exposure may come from a variety of sources; biomarkers that represent a person's recent total arsenic exposure are superior to measurement from a single source. Arsenic's affinity for sulfhydryl groups of keratin causes accumulation where scleroproteins are abundant, such as hair, fingernails, and toenails, which can then be used to quantify a person's exposure. Toenail clippings are an excellent biomarker because they are less susceptible than hair to external contamination, are easy to collect and maintain, and represent long-term exposure (3–12 months prior to collection) (16, 17).

The goal of this case-control study was to examine arsenic content in toenails in relation to cutaneous melanoma.

MATERIALS AND METHODS

Study population

Cutaneous melanoma cases diagnosed in 1999 and 2000 were ascertained through the Iowa Cancer Registry, a population-based registry part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (1). In 1999, 742 cases of melanoma were reported; at the time of case identification, there were 653 cases reported for the year 2000. The fewer number of melanoma cases in 2000 was due to lag time between diagnosis and reporting to the Iowa Cancer Registry. Controls, also identified through the Iowa Cancer Registry, were colorectal cancer patients diagnosed during the same time. Colorectal cancer controls were selected because they are common and have a relatively long survival, and because arsenic exposure has not been conclusively linked to the incidence of colorectal cancer.

Both cases and controls were restricted to those diagnosed with malignant cancer and alive at the time of survey. For comparability, both groups were additionally restricted to Whites aged 40 years or older, since melanoma is predominantly a disease of Whites and few colorectal cancer patients were younger than age 40 years. Of 1,395 melanoma cases diagnosed, 662 met inclusion criteria. Since there were more colorectal cancer cases who met these criteria (n = 2,500), the control group was sampled on the basis of gender and 5-year age group, frequency matching at a one-to-one case-to-control ratio. Not as many persons were diagnosed with colorectal cancer as melanoma between ages 40 and 49 years, so colorectal controls aged 50–59 years were oversampled, effectively making the bottom age stratum for frequency matching age 40–59 years. Additionally, we oversampled controls by 15 percent because of the lower survival rates associated with colorectal cancer. Of the eligible colorectal cancer controls, we randomly selected 776 who met inclusion criteria for contact.

After cases and controls were identified, a letter was sent to the patient's physician asking whether there was a reason that the patient should not be contacted, such as severe illness, mental incompetence, or death. If the physician did not respond within 3 weeks, it was considered passive physician consent to contact the patient. Then, a copy of the survey, a cover letter outlining the study, a toenail collection kit, and an informed consent document were sent to cases and controls. If no response was received within 3 weeks, a reminder letter was sent again asking for participation. After another 3–6 weeks with no response, an attempt was made to contact the subject by telephone. On average, five attempts were made at different times of the day to contact each person for whom a telephone number could be ascertained. Subjects not contacted by telephone, and those contacted who agreed to participate but had misplaced their surveys, were sent another survey and toenail collection packet. The University of Iowa's Institutional Review Board approved this recruitment protocol and all study materials.

Of 662 melanoma cases and 776 colorectal cancer controls initially selected, 12 melanoma patients and 31 colorectal cancer patients were reported deceased by either their physician or a family member. For an additional 15 patients (five melanoma, 10 colorectal), the physician requested that the patient not be contacted because of reasons such as dementia, mental retardation, incarceration, and severe illness. Three controls were removed from our study after completing their surveys because they indicated that their race was other than White (one Asian, two Native American).

Of 645 eligible melanoma cases, 368 responded to the survey (57.1 percent) and 355 provided toenail clippings (55.0 percent). Of 732 eligible colorectal cancer patients, 373 returned the survey (50.9 percent) and 353 submitted toenail clippings (48.2 percent). Overall, of those who returned the survey, 95.5 percent also returned toenail clippings.

Information on eligible nonrespondents was obtained from Iowa Cancer Registry records. Respondents and nonrespondents were similar with respect to gender and stage at diagnosis of their current cancer. They were also similar regarding whether they lived in urban or rural areas ($p = 0.3$). However, respondents were younger than nonrespondents and were more likely to be married. Respondents from both case and control groups were as likely as nonrespondents to have had a prior cancer diagnosis, and that prior cancer diagnosis was more likely to be malignant (compared with in situ) for both groups.

Arsenic exposure assessment

Study participants collected and submitted toenail clippings in provided, prelabeled, plastic bags. Samples were sent to the Exposure Assessment Facility Core of the University of Iowa's Environmental Health Sciences Research Center, where they were washed in acetone to remove dirt and nail polish and were weighed on a microbalance. The weight of samples ranged from 7.2 mg to 855.4 mg (mean, 94.1 mg). Toenail clippings were digested in a nitric acid solution and were placed in a 95°C incubator for 30 minutes or until digestion was complete. Digested samples were analyzed by using graphite furnace atomic absorption

spectrophotometry. The instrument used was a Perkin-Elmer 3300 with HG600 graphite furnace, AS90 autosampler, and an EDL2 external lamp power supply (Perkin-Elmer, Wellesley, Massachusetts).

Samples were compared against a reagent blank and an arsenic standard. The arsenic standard was prepared by using a 1,000-mg/liter arsenic standard solution (Perkin-Elmer). This standard was diluted with 10 percent nitric acid to make a 25-μg/liter solution, which was diluted by the instrument to create a five-point calibration curve ranging from 1.25 μg/liter to 25 μg/liter. The minimum detectable level of arsenic using this method was approximately 2.5 μg/liter. For a 94.1-mg sample, this level corresponds to 0.027 μg of arsenic per gram of toenail.

Statistical analyses

Descriptive analyses were performed for demographic study variables for cases and controls, including frequency distributions and other summary statistics. Log-transformed toenail arsenic concentrations were normally distributed. Cutpoints were set based on quartiles of arsenic concentration in controls. Arsenic was also considered as an ordered categorical variable to test for linear trend. It was presumed that subjects were exposed primarily through their residential water; 44 participants who had changed residences since their diagnosis were excluded from these analyses to reduce misclassification of exposure.

The arsenic content of some toenail samples was below the analytical limit of detection (n = 304), posing the common problem of a left-censored log-normal distribution. Since the actual arsenic concentrations have values between zero and the detection limit, we imputed values for these samples by assigning them the minimum detectable limit divided by the square root of 2, a method often referred to as triangular approximation (18).

Unconditional logistic regression was used to examine melanoma in relation to toenail arsenic levels (19). All analyses controlled for any residual confounding due to age, gender, and education. For arsenic content, we assessed effect modification by history of sunburn, prior cancer diagnosis, prior skin cancer diagnosis, and time at the current residence. If no effect modification was seen, potential confounding was assessed for these factors as well as for skin color and skin type. Confounding was determined by a 10 percent or more change in the odds ratio.

Residential water source and occupation were explored as potential sources of exposure. For those who used private wells as their primary source of water, well depth was considered with respect to arsenic concentration. Occupations in which subjects worked with wood treated with chromium copper arsenate or those potentially involved in arsenical pesticide production and application industries were considered at risk for occupational exposure to arsenic (4). Industries that traditionally involve high arsenic exposures, such as copper smelting, are not common in Iowa (4). Because of the low prevalence of these occupations and because we did not measure actual arsenic levels on the job, we classified participants as potentially exposed to arsenic if they reported employment in industries that had the possibility for arsenic exposure, such as farming, carpentry, construction, golf course maintenance, or lumber yard work. Participants with a high arsenic toenail concentration were compared with those with a low concentration based on their employment in these fields and with respect to self-reported occupational arsenic exposure.

TABLE 1. Distribution of selected demographic factors among participating melanoma cases and colorectal cancer controls in Iowa, 1999–2000

	Cases (n = 368)		Controls (n = 373)	
	No.	%	No.	%
Age (years)				
40–49	96	26.1	59	15.8
50–59	84	22.8	111	29.8
60–69	85	23.1	106	28.4
70–79	72	19.6	68	18.2
80–89	31	8.4	29	7.8
	χ^2 p = 0.005			
Gender				
Male	205	55.7	240	64.3
Female	163	44.3	133	35.7
	χ^2 p = 0.016			
Education*				
Less than high school	40	11.0	33	9.0
High school graduate	114	31.4	166	45.0
More than high school	209	57.6	169	46.0
	χ^2 p = 0.0007			
Marital status				
Never married	18	4.9	17	4.6
Married	288	78.3	293	78.6
Divorced/separated	25	6.8	20	5.3
Widowed	37	10.0	43	11.5
	χ^2 p = 0.79			

* Numbers do not sum to total because of missing information.

RESULTS

Compared with controls, melanoma cases were younger and were significantly more likely to be female (table 1). The median age was 60 years (range, 40–97 years) for cases and 62 years (range, 40–91 years) for controls. Approximately 78 percent of both groups were married. Cases were more likely to have a post-high-school education. Melanoma was associated with sunburn history (odds ratio (OR) = 2.1 for childhood, 95 percent CI: 1.3, 3.6; OR = 1.8 for adolescence, 95 percent CI: 1.0, 3.2; and OR = 2.9 for adulthood, 95 percent CI: 1.7, 5.0) and sun sensitivity (OR = 1.4 for fair skin, 95 percent CI: 1.0, 2.1 and OR = 1.7 for tendency to burn, 95 percent CI: 0.9, 3.4).

For all analyses associated with arsenic, 44 participants (24 cases, 20 controls) who had moved since diagnosis were

TABLE 2. Risk of arsenic exposure and cutaneous melanoma, Iowa, 1999–2000

Toenail arsenic content (μg/g)	Cases (n = 326)		Controls (n = 329)		OR*,†	95% CI*
	No.	%	No.	%‡		
≤0.020	52	16.0	82	24.9	1.0	
0.021–0.039	58	17.8	83	25.2	1.0	0.6, 1.6
0.040–0.083	95	29.1	82	24.9	1.7	1.1, 2.7
≥0.084	121	37.1	82	24.9	2.1	1.4, 3.3
					p-trend = 0.001	

* OR, odds ratio; CI, confidence interval.
† Adjusted for age, gender, and education.
‡ Percentages do not total 100 because of rounding.

excluded. An additional nine samples were excluded (five from cases, four from controls) because of laboratory quality control problems. On average, controls submitted larger toenail clippings than did cases (100.7 mg vs. 87.4 mg), but cases and controls were similar regarding mean years at their current residence (22.2 years for cases and 21.6 years for controls). The median arsenic concentration was 0.060 μg of arsenic per gram of toenail for cases (5th and 95th percentiles at 0.013 μg/g and 0.359 μg/g) and 0.040 μg of arsenic per gram of toenail for controls (5th and 95th percentiles at 0.012 μg/g and 0.313 μg/g). The geometric mean was similar to the median for both cases and controls.

The association between toenail arsenic concentration and melanoma showed a significant increasing linear trend with increasing toenail arsenic concentration (table 2). The odds ratio for the highest quartile of arsenic concentration compared with the lowest was 2.1 (95 percent CI: 1.4, 3.3). No confounding by skin color, skin type, or prior history of sunburn was found. We did see a significant effect modification between arsenic content and risk of melanoma by self-reported prior skin cancer diagnosis (table 3). Risk of melanoma with increasing toenail arsenic content was much greater for those with a prior skin cancer diagnosis (OR = 6.6, 95 percent CI: 2.0, 21.9) than for those without (OR = 1.7, 95 percent CI: 1.0, 2.8). When we stratified by time at the current residence (table 4), elevated odds ratios were found for the highest arsenic exposure category for those who had lived at their current residence less than 15 years (OR = 2.8, 95 percent CI: 1.4, 5.8) as well as for those who had lived there for 15 years or more (OR = 1.8, 95 percent CI: 1.0, 3.4). Similar results were found when stratifying by less than 10, 10–19, and 20 years or longer at the current residence.

TABLE 3. Risk of arsenic exposure and cutaneous melanoma by self-reported prior skin cancer diagnosis, Iowa, 1999–2000

Toenail arsenic content (μg/g)	No prior skin cancer diagnosis (n = 519)		Prior skin cancer diagnosis (n = 130)	
	OR*,†	95% CI*	OR†	95% CI
≤0.020	1.0		1.0	
0.021–0.039	0.8	0.5, 1.4	2.5	0.8, 7.8
0.040–0.083	1.3	0.8, 2.3	3.9	1.4, 11.4
≥0.084	1.7	1.0, 2.8	6.6	2.0, 21.9
	p-trend = 0.0087		p-trend = 0.001	
	p-interaction = 0.03			

* OR, odds ratio; CI, confidence interval.
† Adjusted for age, gender, and education.

The potential source of arsenic was explored by examining water source and possible occupational exposure. Table 5 describes type of water supply for cases and controls. There was some suggestion of an increased risk for those who used private wells (OR = 1.4, 95 percent CI: 1.0, 2.1).

Participants with the highest toenail arsenic concentration were more likely to use private wells than were those with the lowest arsenic concentrations, regardless of case-control status (table 6). The number of participants who reported they had been exposed to arsenic on the job was low (n = 23). Of these, 14 were in the highest arsenic category compared with only three in the lowest (table 6), indicating that occupational exposure may be an important source of arsenic contamination for a small portion of the study population. On the basis of occupational classification, those at risk of arsenic exposure included anyone who reported working in carpentry, construction, farming, golf course maintenance, or a lumberyard (table 6). Subjects in the highest quartile of arsenic concentration were more likely to be in these high-risk occupations than were those in the lowest quartile (7.0 percent vs. 2.3 percent).

DISCUSSION

We found an elevated risk of cutaneous melanoma with increasing arsenic concentration in toenail clippings. Exposure to arsenic has consistently been shown to be associated with other skin cancer, such as basal and squamous cell carcinoma (3, 8–10). To our knowledge, this association has not been previously reported in observational studies of cutaneous melanoma incidence. One possible explanation may be that most previous studies examining melanoma incidence in association with arsenic exposure were conducted

TABLE 4. Risk of arsenic exposure and cutaneous melanoma stratified by length of time at the current residence, Iowa, 1999–2000

Toenail arsenic content (μg/g)	Cases (n = 142)		Controls (n = 139)		OR*,†	95% CI*
	No.	%	No.	%		
Lived at the current residence <15 years						
≤0.020	18	12.7	34	24.5	1.0	
0.021–0.039	21	14.8	32	23.0	1.2	0.5, 2.6
0.040–0.083	43	30.3	35	25.2	2.2	1.1, 4.6
≥0.084	60	42.2	38	27.3	2.8	1.4, 5.8
					p-trend = 0.001	
	Cases (n = 184)		Controls (n = 190)			
	No.	%	No.	%		
Lived at the current residence ≥15 years						
≤0.020	34	18.5	48	25.3	1.0	
0.021–0.039	37	20.1	51	26.8	1.0	0.5, 1.8
0.040–0.083	52	28.3	47	24.7	1.5	0.8, 2.8
≥0.084	61	33.1	44	23.2	1.8	1.0, 3.4
					p-trend = 0.01	
			p-interaction = 0.3			

* OR, odds ratio; CI, confidence interval.
† Adjusted for age, gender, and education.

in Asian countries (8, 10), where risk of melanoma is much lower than it is in Caucasian populations (20). The effect of arsenic on melanoma risk may be modified by genetic or constitutional factors, such as skin color and sun sensitivity. Therefore, etiology of melanoma in these Asian populations is likely to be different than in Caucasians. Although we did not find that the effect of arsenic was modified by sun sensitivity and skin color, our study was restricted to Caucasians. The strength of association (OR = 2.1) and statistically significant dose-response relation seen in this study indicate that this connection may support a causal relation. The association was modified by prior skin cancer diagnosis, further supporting a potential causal association between arsenic and cutaneous melanoma.

TABLE 5. Type of water supply and risk of cutaneous melanoma, Iowa, 1999–2000*

	Cases (n = 368)		Controls (n = 373)		OR†,‡	95% CI†
	No.	%	No.	%		
Drinking water source						
Community supply	249	73.0	275	78.6	1.0	
Private well	74	21.7	59	16.8	1.4	1.0, 2.1
Bottled water	18	5.3	16	4.6	1.1	0.5, 2.2
Depth of private well						
Used community supply	249	77.1	275	82.1	1.0	
≥100 feet§	45	13.9	30	9.0	1.6	1.0, 2.7
50–99 feet	15	4.6	10	3.0	1.8	0.8, 4.0
<50 feet	7	2.2	8	2.4	1.1	0.4, 3.1
Unknown	7	2.2	11	3.5	0.8	0.3, 2.0

* Numbers do not sum to total because of missing information.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age, gender, and education.
§ One foot = 0.3 m.

TABLE 6. Arsenic toenail concentration in relation to type of drinking water supply and occupational exposure of study participants, Iowa, 1999–2000

	Total		Mean toenail arsenic concentration (μg/g)	Toenail arsenic concentration ≥0.084 μg/g		Toenail arsenic concentration ≤0.020 μg/g	
	No.	%		No.	%	No.	%
Type of water supply							
Community supply	494	75.8	0.09	142	70.3	110	82.1
Private well	126	19.3	0.12	48	23.8	22	16.4
Bottled water	32	4.9	0.12	12	5.9	2	1.5
					χ^2 p = 0.025		
Depth of private well*							
≥100 feet†	71	56.3	0.06	25	52.1	9	40.9
50–99 feet	22	17.5	0.10	9	18.8	3	13.6
<50 feet	15	11.9	0.12	3	6.2	6	27.3
					χ^2 p = 0.059		
Unknown	18	14.3	0.15	11	22.9	4	18.2
Self-reported occupational arsenic exposure							
No known occupational exposure	536	83.0	0.09	152	76.0	113	85.6
Known occupational exposure	23	3.5	0.14	14	7.0	3	2.3
					χ^2 p = 0.042		
Unknown occupational exposure	87	13.5	0.11	34	17.0	16	12.1
Usual job							
Low arsenic risk	615	93.9	0.10	187	92.1	129	96.3
High arsenic risk‡	40	6.1	0.17	16	7.9	5	3.7
					χ^2 p= 0.064		

* Numbers do not sum to total because of missing information.

† One foot = 0.3 m.

‡ High-arsenic-risk job defined as carpenter, construction worker, farmer, golf course maintenance worker, or lumberyard worker.

The use of a biomarker accounting for arsenic from all sources eliminates the need for participants to recall their exposures, thereby reducing the potential for recall bias. However, collection 2–3 years after diagnosis presents a limitation of this technique in a case-control study. We cannot discount the possibility that misclassification of exposure to arsenic occurred because of changing exposures postdiagnosis. In this study, the average length of time that subjects lived at their current location was 21.9 years. If the latency period for arsenic is shorter than 20 years, and if people are exposed primarily through their drinking water, it seems likely we would have captured the relevant period of arsenic exposure. We stratified our analyses to investigate a potential difference in risk based on time at the current residence. We observed no effect modification by time at the current residence and found elevated odds ratios for the highest exposure in both time periods. The mean length of time at the current residence was over 20 years. However, it is possible that the source of water could have changed while residence remained constant, meaning that arsenic exposure through drinking water could be more variable than suggested by time at the current residence.

Increased postdiagnosis arsenic levels in melanoma cases are unlikely to be related to treatment. The preferred course of treatment for melanoma is surgical excision (21, 22). Chemotherapeutic drugs for melanoma treatment include dacarbazine, interferon, cisplatin, tamoxifen, and carmustine (23, 24). These therapies are not known to contain arsenic, making it unlikely that increased arsenic levels in melanoma cases are due to treatment.

When compared with subjects using community supplies as their water source, those using private wells were more likely to have toenail arsenic concentrations in the highest quartile than in the lowest. Private wells are not subject to the same requirements for testing as are public water supplies, leading to the possibility of undetected contamination. In a New Hampshire study, private wells were associated with higher levels of arsenic than were public water

supplies (25). That study also showed a correlation between arsenic levels in the residential water supply and toenail arsenic concentrations. The amount of arsenic in the toenail that corresponds to particular concentrations in drinking water is unknown and likely depends on the amount of water consumed and exposure to other sources of arsenic. In the New Hampshire study, 1 μg of arsenic per liter of water corresponded to approximately 0.1 μg of arsenic per gram of toenail. A doubling of toenail arsenic concentration was associated with a 10-fold increase in water arsenic in those samples at or above 1 μg/liter (25).

Although water supplies are presumed to be the most common means by which study participants are exposed to arsenic, occupational exposures may be important in a subsample of this population. In our study, over twice as many subjects in the highest quartile of arsenic exposure had reported a known occupational exposure to arsenic than those in the lowest quartile. Additionally, those classified as being in higher risk jobs were more likely to be in the highest quartile of arsenic concentration than in the lowest.

This study had several strengths. Cases and controls were ascertained through the Iowa Cancer Registry, a Surveillance, Epidemiology, and End Results Program registry. This registry enabled population-based ascertainment of newly diagnosed melanoma cases in a specified time period and a high degree of certainty about accuracy of diagnosis. Colorectal cancer controls were selected from the same registry and came from the same underlying population. Toenail arsenic levels are not susceptible to recall bias and are used to estimate total body burden. Concentration has been shown to be relatively stable; a reproducibility study of trace elements in toenails found arsenic levels to be highly correlated over a 6-year follow-up (26).

Our study found an increased risk of melanoma with history of sunburn and sun sensitivity factors, with observed odds ratios in the range of 1.4–2.9, which concurs with other studies of conventional risk factors for melanoma (27–32). This similarity of findings lends credibility to other results we found concerning melanoma and arsenic.

The primary limitation of this study is comparison of melanoma cases with cancer controls. Cancer controls were chosen because of the difficulty in ascertaining appropriate population-based controls. Use of driver's license records has traditionally been a good way to identify controls (33), but this method has changed recently because of a federal law restricting access to department of motor vehicle records for research purposes (34). Limited funding also played a role in our selection of colorectal cancer controls. We are unaware of any studies linking colorectal cancer incidence to arsenic exposure. We were unable to find literature suggesting that arsenic absorption was affected either by colorectal cancer itself or by common treatment drugs. We were also unable to find any evidence that the disease or its treatment affected toenail loss. In our analyses, we saw no differences in toenail arsenic concentration by treatment. One early study did report an association of arsenic exposure with colorectal cancer mortality (8), but several other studies have failed to find a similar increase, although these studies were smaller in number than the original (35–39). We chose to use only one cancer site as a control group because of the difficulty identifying another cancer site that was not associated with arsenic or sun exposure, included an adequate number of cases, and had a relatively good survival rate since we were contacting people 2–3 years after diagnosis.

Another concern with this group was the older age of the controls. Since age was not correlated with arsenic concentration, this age difference was probably not a factor in the observed association with arsenic. Although we frequency matched on gender when recruiting participants for this study, males in the control group were more likely to participate than were females, resulting in a greater number of females in the case group than in the control group. Arsenic concentration was not correlated with gender.

An additional drawback of using cancer controls is the possibility that risk factors of interest are also associated with disease in controls. If this scenario were to occur, it would bias results toward the null. For our results to be biased because of use of colorectal cancer cases, colorectal cancer would have to be inversely associated with arsenic exposure. Arsenic is recognized as a human carcinogen; therefore, it is unlikely to be protective for colorectal cancer (40).

The relatively low response rate (53.2 percent overall) is another limitation of this study. This limitation could have led to nonresponse bias if respondents had different exposures than nonrespondents, which could bias results in either direction. For arsenic, there is no reason to believe that respondents and nonrespondents were more or less likely to be exposed. According to the Iowa Department of Natural Resources, the percentage of Iowans using some source other than public supplies for their water was comparable between our study (15.8 percent) and the Iowa general population (14.2 percent), indicating that our control group was similar to the general population (41). Additionally, respondents and nonrespondents were similar with respect to living in urban or rural areas. Therefore, nonresponse bias should be less of a concern for these analyses. Nonrespondents were significantly older than respondents in this study. There was potential for survival bias, since participation in the study was restricted to those people still living. This bias could occur if the exposure of interest is related to a more virulent disease process, thereby causing death from melanoma at a more rapid rate than would otherwise occur. Exclusion of these cases would therefore have biased results toward the null, and the association found here would likely be an underestimate of the true magnitude. Conversely, in the unlikely event that arsenic is associated with a more virulent form of colorectal cancer, gathering information from only living cases would result in an overestimation of the association with melanoma.

In summary, to our knowledge, the association between increasing arsenic exposure and cutaneous melanoma risk has not been previously reported and is important because of the potential for large numbers of people to be exposed to arsenic. We observed an even higher effect among those with a prior nonmelanoma skin cancer diagnosis, which lends further support to a causal association between arsenic and cutaneous melanoma. In Iowa, use of private wells for residential drinking water appeared to be associated with both increased toenail arsenic content and increased melanoma risk. While it

appears that water supplies are the means by which most persons are exposed to arsenic, the possibility of occupational exposure to arsenic cannot be excluded. The association we observed with arsenic is not known to have been previously reported in observational studies of incident cutaneous melanoma. Therefore, the findings warrant confirmation.

ACKNOWLEDGMENTS

This study was supported by National Institute of Environmental Health Sciences (NIEHS) grant P30 ES05605. Dr. Beane Freeman was supported as a National Research Service Award Trainee through the Environmental Health Sciences Training Program (NIEHS T32 ES07314).

REFERENCES

1. Ries LAG, Eisner MP, Kosary CL, et al. SEER cancer statistics review, 1975–2000. Bethesda, MD: National Cancer Institute, 2003. (http:/seer.cancer.gov/csr/1975_2000).
2. Morton WE, Dunnette DA. Health effects of environmental arsenic. In: Nriagu JO, ed. Arsenic in the environment. Part II: human health and ecosystem effects. New York, NY: John Wiley & Sons, 1994.
3. Hsueh YM, Cheng GS, Wu MM, et al. Multiple risk factors associated with arsenic-induced skin cancer: effects of chronic liver disease and malnutritional status. Br J Cancer 1995;71:109–14.
4. Agency for Toxic Substances and Disease Registry. Toxicological profile for arsenic. Atlanta, GA: Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services, 2000. (Publication CAS#7440-38-2).
5. Gebel T. Confounding variables in the environmental toxicology of arsenic. Toxicology 2000;144:155–62.
6. VanDorpe P. Arsenic in Iowa's municipal water supplies. Iowa Groundwater Q 2000;11:13–19.
7. Ryker SJ. Mapping arsenic in groundwater. Geotimes 2001;46:34–6.
8. Chen CJ, Chuang YC, Lin TM, et al. Malignant neoplasms among residents of a Blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. Cancer Res 1985;45:5895–9.
9. Karagas MR, Stukel TA, Morris JS, et al. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. Am J Epidemiol 2001;153:559–65.
10. Tseng WP, Chu HM, How SW, et al. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst 1968;40:453–63.
11. Pesch B, Ranft U, Jakubis P, et al. Environmental arsenic exposure from a coal-burning power plant as a potential risk factor for nonmelanoma skin carcinoma: results from a case-control study in the district of Prievidza, Slovakia. Am J Epidemiol 2002;155:798–809.
12. Woodhead AD, Setlow RB, Tanaka M. Environmental factors in nonmelanoma and melanoma. J Epidemiol 1999;9(6S):S102–14.
13. Smith AH, Hopenhayn-Rich C, Bates MN, et al. Cancer risks from arsenic in drinking water. Environ Health Perspect 1992;97:259–67.
14. Lewis DR, Southwick JW, Oullet-Hellstrom R, et al. Drinking water arsenic in Utah: a cohort mortality study. Environ Health Perspect 1999;107:359–65.
15. Watanabe C, Inaoka T, Kadono T, et al. Males in rural Bangladeshi communities are more susceptible to chronic arsenic poisoning than females: analyses based on urinary arsenic. Environ Health Perspect 2001;109:1265–70.
16. Schroeder H, Balassa JJ. Abnormal trace metals in man: arsenic. J Chronic Dis 1966;19:85–106.
17. Henke G, Nucci A, Quieroz L. Detection of repeated arsenical poisoning by neutron activation analysis of foot nail segments. Arch Toxicol 1982;50:125–31.
18. Hornung RW, Reed LD. Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 1990;5:46–51.
19. Hosmer DW, Lemeshow S. Applied logistic regression. New York, NY: John Wiley & Sons, 1989.
20. Urist M, Miller D, Maddox W. Malignant melanoma. In: Murphy G, Lawrence W, Lenhard R, eds. American Cancer Society textbook in clinical oncology. Atlanta, GA: American Cancer Society, 1995.
21. McCarthy WH, Shaw HM. The surgical treatment of primary melanoma. Hematol Oncol Clin North Am 1998;12:797–805.
22. Wagner JD, Gordon MS, Chuang TY, et al. Current therapy of cutaneous melanoma. Plast Reconstr Surg 2000;105:1774–99.
23. Pavlick AC. Chemotherapy approaches to melanoma. Dermatol Clin 2002;20:709–12.
24. Sun W, Schuchter LM. Metastatic melanoma. Curr Treat Options Oncol 2001;2:193–202.
25. Karagas MR, Tosteson TD, Blum J, et al. Measurement of low levels of arsenic exposure: a comparison of water and toenail concentrations. Am J Epidemiol 2000;152:84–90.
26. Garland M, Morris JS, Rosner BA, et al. Toenail trace element levels as biomarkers: reproducibility over a 6-year period. Cancer Epidemiol Biomarkers Prev 1993;2:493–7.
27. Holly EA, Kelly JW, Shpall SN, et al. Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol 1987;17:459–68.
28. Beitner H, Norell SE, Ringborg U, et al. Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. Br J Dermatol 1990;122:43–51.
29. Beral V, Evans S, Shaw H, et al. Cutaneous factors related to the risk of malignant melanoma. Br J Dermatol 1983;109:165–72.
30. Holman CDJ, Armstrong BK. Pigmentary traits, ethnic origin, benign nevi and family history as risk factors for cutaneous malignant melanoma. J Natl Cancer Inst 1984;72:257–66.
31. Elwood JM, Gallagher RP, Hill GB, et al. Cutaneous melanoma in relation to intermittent and constant sun exposure: the Western Canada melanoma study. Int J Cancer 1985;35:427–33.
32. Dubin N, Moseson M, Pasternack BS. Epidemiology of malignant melanoma: pigmentary traits, ultraviolet radiation, and the identification of high risk populations. Recent Results Cancer Res 1986;102:56–75.
33. Lynch CF, Logsden-Sackett N, Edwards SL, et al. The driver's license list as a population-based sampling frame in Iowa. Am J Public Health 1994;84:469–72.
34. Adimora AA, Schoenbach VJ, Martinson FE, et al. Driver's license and voter registration lists as population-based sampling frames for rural African Americans. Ann Epidemiol 2001;11:385–8.
35. Luchtrath H. The consequences of chronic arsenic poisoning among Moselle wine growers: pathoanatomical investigations of post-mortem examinations performed between 1960 and 1977. J Cancer Res Clin Oncol 1983;50:173–82.
36. Chen CJ, Wang CJ. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant melanoma. Cancer Res 1990;50:5470–4.

37. Cuzick J, Evans S, Gillman M, et al. Medicinal arsenic and internal malignancies. Br J Cancer 1982;45:904–11.
38. Tsuda T, Babazono A, Yamamoto E, et al. Ingested arsenic and internal cancer: a historical cohort study followed for 33 years. Am J Epidemiol 1995;141:198–209.
39. Wu MM, Kuo TL, Hwang YH, et al. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am J Epidemiol 1989;130: 1123–32.
40. Cantor KP, Shy CM, Chilvers C. Water pollution. In: Schottenfeld D, Fraumeni JF, eds. Cancer epidemiology and prevention. New York, NY: Oxford University Press, 1996.
41. State of Iowa Public Drinking Water Program. 2001 annual compliance report. Des Moines, IA: Iowa Department of Natural Resources–Environmental Protection Division, Water Quality Bureau, Drinking Water Supply Section, 2002. (http://www.state.ia.us/government/dnr/organiza/epd/wtrsuply/report/01/01final.pdf).